Journal of Forensic and Legal Medicine 20 (2013) 74–85

Contents lists available at SciVerse ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Review

Mechanisms of chronic pain from whiplash injury

Charles G. Davis B.S., D.C., Private practice

417-B W. Foothill #401, Glendora, United States

ARTICLE INFO

Article history:
Received 21 December 2011
Received in revised form
3 May 2012
Accepted 30 May 2012
Available online 4 July 2012

Keywords:
Whiplash injury
Chronic pain
Neck pain
Hypersensitivity
Nociception
Neuropathic

ABSTRACT

This article is to provide insights into the mechanisms underlying chronic pain from whiplash injury. Studies show that injury produces plasticity changes of different neuronal structures that are responsible for amplification of nociception and exaggerated pain responses. There is consistent evidence for hypersensitivity of the central nervous system to sensory stimulation in chronic pain after whiplash injury. Tissue damage, detected or not by the available diagnostic methods, is probably the main determinant of central hypersensitivity. Different mechanisms underlie and co-exist in the chronic whiplash condition. Spinal cord hyperexcitability in patients with chronic pain after whiplash injury can cause exaggerated pain following low intensity nociceptive or innocuous peripheral stimulation. Spinal hypersensitivity may explain pain in the absence of detectable tissue damage. Whiplash is a heterogeneous condition with some individuals showing features suggestive of neuropathic pain. A predominantly neuropathic pain component is related to a higher pain/disability level.

1. Introduction

This is a review of studies focusing on the mechanisms of pain from whiplash injury. Whiplash is an acceleration-deceleration mechanism of energy transfer to the spine. The injury is caused by a rapid change in the position of the head which imparts energy transfer to the structures of the cervical spine, most commonly as a result of an automobile accident. The energy transfer may result in bony or soft tissue injuries, which in turn may lead to a wide variety of clinical manifestations (whiplash-associated disorders - WAD). The distinction between acute and chronic pain has traditionally been determined by an arbitrary interval of time since onset; the two most commonly used markers being 3 months and 6 months since onset.[1] Neck and back injury are independent of crash severity and may occur at low speeds.[2–6] When stimulus intensity is high enough, receptors are activated in the peripheral endings of primary afferents. Mechanical, thermal, and chemical stimuli are detected by nerve endings called nociceptors. The majority of nociceptors can be activated by several types of sensory inputs [thermal, mechanical, and chemical] and are therefore termed polymodal nociceptors. Nociceptors are sensory small-diameter, slow conducting, predominantly unmyelinated [C-fibers] or thinly myelinated [Aδ-fibers] neurons.[7,8] The cell bodies of these primary afferents, which are located in the dorsal root ganglia, project their proximal nerve terminals mainly to the laminae I–II of the spinal cord dorsal horn.[8] Tissue injury, which is commonly the immediate cause of pain, results in a local release or synthesis of a range of substances such as Bradykinins and Prostaglandins, substance P [SP] and Calcitonin-gene-related peptide [CGRP], and thereby interact with adjacent immune cells and blood vessels in a complex manner.[9]

It has been noted by numerous researchers that chronic whiplash patients have different sensory thresholds than normal controls.[10–15] Whiplash injury has been shown to damage the facet joint by compression and/or stretching and to the intervertebral disc by shearing forces. Injury to the vertebral joints, including the discs and facets, produces nociceptive type of pain, and/or neurogenic/neuropathic type of pain [pain arising from nervous system]. Transmission of pain from the periphery to the cortex depends on integration and signal processing within the spinal cord, brainstem, and forebrain. Sensitization, a component of persistent or chronic pain, may develop either through peripheral mechanisms or as a consequence of altered physiology in the spinal cord or forebrain. Several mechanisms contribute to the phenomenon of sensitization and persistent pain, including upregulation of sensory neuron receptors, phenotypic switching of large myelinated axons, sprouting within the dorsal horn, and loss of inhibitory neurons. Abnormal pain perception in the affected regions of these patients includes three different components: spontaneous continuous pain [usually burning and aching in quality], spontaneous intermittent pain [usually stinging in quality] and abnormally evoked pain

E-mail address: cdavisdc@yahoo.com.

1752-928X/$ – see front matter © 2012 Elsevier Ltd and Faculty of Forensic and Legal Medicine. All rights reserved.
http://dx.doi.org/10.1016/j.jflm.2012.05.004

[usually produced by touch or movement]. Stimulus-evoked pain may be abnormal leading to allodynia [pain produced by normally non-painful stimulation], hyperalgesia [an overreaction to a stimulus which is normally painful] or hyperpathia [occurs on neuropathic pain patients with the loss of fibers and is a greatly exaggerated pain sensation to nociceptive stimuli]. Prior research on psychosocial causes of chronic pain following whiplash are likely confounded because of a failure to account for a possible neuropathologic/neurophysiological basis for the symptoms.[16–18] This article addresses different mechanisms that may be the cause of chronic pain that may occur after a whiplash injury.

1.1. Methods

Sources used for this review include reviews of the literature of animal and human studies focusing on the mechanisms of post injury central sensitization, an analysis of neurophysiological investigations on central hypersensitivity in patients with chronic pain after whiplash injury. A search of anatomical structures arising from whiplash injury was performed. The chiropractic, orthopedic, physical medicine, neurophysiology and pain management fields were searched using the following citation indices: criteria for the literature search English language, peer-reviewed, non-commentary, PubMed through Medline, Google's scholar "scientific" search engine, pain and whiplash texts. Key words used were; whiplash injury, chronic pain, neck pain, hypersensitivity, nociception, neuropathic.

2. Discussion

Whiplash injury has been shown to damage deep tissues in the facet joint by compression and/or stretching and to the disc by shear forces. The cervical facet capsular ligaments may be injured under combined shear, bending, and compression load levels that occur in rear-end impacts.[19–22] Cervical facet capsular ligaments may be injured under loading conditions similar to those generated during whiplash [rear-end 8 km per hour [5 miles per hour] rear-end collision].[20] Findings indicate that facet capsule strains (Strain is defined as the amount of deformation per unit length of an object when a load is applied. Strain is calculated by dividing the total deformation of the original length by the original length (L): Strain (ε) = (ΔL/L) comparable to those previously reported for whiplash kinematics and incomplete failures of this ligament have the potential to produce pain symptoms and alter one element of nociception. Allodynia results showed immediate and sustained behavioral sensitivity following subfailure vertebral distractions; pain symptoms were significantly greater than those for other injury groups. Further, spinal astrocytic activation was also greater for subfailure injuries compared to lower distraction magnitudes.[23,24] (Table 1).

Table 1
Types of pain.

Nociceptive pain: Physiological pain produced by noxious stimuli that activate high-threshold nociceptor neurons.
Inflammatory pain: Pain hypersensitivity due to peripheral tissue inflammation involving the detection of active inflammation by nociceptors and a sensitization of the nociceptive system.
Dysfunctional pain [fibromyalgia syndrome]: Amplification of nociceptive signaling in the absence of either inflammation or neural lesions.
Neuropathic pain: Maladaptive plasticity caused by a lesion or disease affecting the somatosensory system altering nociceptive signal processing so that pain is felt in the absence of a stimulus, and responses to innocuous and noxious stimuli are enhanced.[25]

xA neuropathic type of pain may arise from neck and back complaints in approximately 30% of cases.[26,27] There are at least six main mechanisms involved in neuropathic pain becoming chronic [28]:

1. activity increase in areas of the pain neuromatrix
2. recruitment of additional cortical areas beyond the classical pain neuromatrix
3. cortical reorganization and maladaptive neuroplasticity
4. alterations in neurochemistry
5. structural brain changes
6. disruption of the brain default mode network

2.1. Injury mechanisms

The cervical facet capsular ligaments may be injured under combined shear, bending, and compression load levels that occur in rear-end impacts.[22] Facet joint components are at risk for injury during whiplash due to facet joint compression and excessive capsular ligament strain.[20]

The pinching of the lower cervical facet joints may lead to local tissue injury and nociceptive pain.[21] Cervical facet capsular ligaments may be injured under loading conditions similar to those generated during whiplash [rear-end 8 km per hour [5 miles per hour] rear-end collision].[22] There does not need to be a complete failure of the tissues to cause injury or pain. Findings indicate that facet capsule strains comparable to those previously reported for whiplash kinematics and subcatastrophic failures of this ligament have the potential to produce pain symptoms and alter one element of nociception. Abnormal pain sensations (i.e. allodynia) results showed immediate and sustained behavioral sensitivity following subfailure vertebral distractions as pain symptoms were significantly greater than those for other injury groups. Further, spinal astrocytic activation was also greater for incomplete injuries compared to lower distraction magnitudes.[20] When compared to the reported strains that facet joint capsules experienced in whiplash [35–60 percent] and the reported capsule subfailure strains [35–67 percent], high thresholds and after discharge strains are within that range.[20] High threshold units likely signal nociception [pain sensation] while after discharge may signal capsule strain injury and contribute to persistent pain.[23] Mechanical findings provide insight into the relationship between gross structural failure and painful loading for the facet capsular ligament. The ligament yield point occurred at a distraction magnitude in which pain symptoms begin to appear.[29] Stretching the facet joint capsule beyond physiological range could result in altered axonal morphology that may be related to secondary or delayed axotomy changes similar to those seen in central nervous system injuries where axons are subjected to stretching and shearing. These may contribute to neuropathic pain and are potentially related to neck pain after whiplash events.[30]

Injured somatic tissues adjacent to nerve structures release inflammatory substances that can chemically irritate neural tissues.[31–36] Inflammatory cytokines (interleukin [IL]-1beta, tumor necrosis factor [TNF] alpha and IL-6 may be responsible for the genesis of pain production in the facets[37,38] and IL-6, IL-8, prostaglandin E2, matrix metalloproteinases, and nitric oxide in disc herniations.[39–41] Prostaglandins can block endogenous opioid-mediated analgesia systems by inhibiting the bulbospinal noradrenergic component of this analgesia pathway.[42]

Chronic pain resulting from low-speed collisions may be explained by partial tears of soft tissues including annular fibers, ligaments, and avascular cartilage. Because of poor blood supply, these tissues may not completely heal following injury. Resulting

injuries produce altered cervical spine kinematics that can lead to accelerated degenerative changes and clinical instability.[43]

Both animal and human studies have demonstrated structural damage from whiplash type injuries. In different species of monkeys, experimentally caused acceleration/extension injuries have revealed a variety of lesions: muscle tears, avulsions, and hemorrhages; rupture of the anterior longitudinal and other ligaments, especially between C4 and C7; avulsions of disc from vertebral bodies and disc herniations; retropharyngeal hematoma; intralaryngeal and esophageal hemorrhage; cervical sympathetic nerve damage associated with damage to the longus colli; nerve root injury; cervical spinal cord contusions and hemorrhages; cerebral concussion; and gross hemorrhages and contusions over the surface of the cerebral hemispheres, brainstem, and cerebellum.[44,45]

Magnetic resonance image study of patients done within four months of the whiplash type injury revealed ruptures of the anterior longitudinal ligament, horizontal avulsion of the vertebral end plates, separation of the disc from the vertebral end plate, occult fractures of the anterior vertebral end plate, acute posterolateral cervical disc herniations, focal muscular injury of the longus colli muscle, posterior interspinous ligament injury, and prevertebral fluid collections. Autopsy series have shown injuries similar to those in the animal studies, including injuries to intervertebral discs and soft tissue injuries of facet joints.[46,47,219]

2.2. Facets and discs

Both discs and facet joints can be injured in whiplash. Research indicates that the source of the pain in a majority (~60%) of whiplash patients is the zygapophyseal (facet) joints.[48] The facet synovial folds are pain sensitive.[49,50] A common disc injury is a "rim lesion" or transverse tear near the anterior vertebral rim. It is caused by distraction and shearing in sudden extension. Both the posterior disc and the facets are compressed, causing disc contusion or herniation, facet hemarthrosis, bruising around the C2 nerve, or fractures of articular processes. Suboccipital vascular congestion and annulus calcification are also seen. Chronic pain develops in 20–40 percent. The reasons include altered spinal mechanics, neural damage and vascular changes.[51]

Management must always start with an accurate diagnosis based on a history and physical examination. Simple investigations such as extension x-rays may reveal vacuum clefts in the same anatomical position as rim lesions. Nuclear scans detect increased uptake at damaged end plates or facet fractures.[52] The facet joints are abundantly innervated with Aδ-and C-nerve fibers that operate at a high threshold and may become sensitized or excited by local pressure changes, capsular stretching, and naturally occurring proinflammatory agents [e.g., SP, phospholipase A, and IL-1β].[38,53–56] Studies have documented the presence of cervical disc injury in 20–25 percent of subjects following whiplash injury, and these findings can correlate with radicular symptoms.[57,58]

2.3. Ligaments

These results indicate that symptoms and complaints among whiplash associated disorder [WAD] patients can be linked with structural abnormalities in ligaments and membranes in the upper cervical spine, in particular the alar ligaments. Whiplash patients who had been sitting with their head/neck turned to one side at the moment of collision more often had high-grade lesions of the alar and transverse ligaments. Severe injuries to the transverse ligament and the posterior atlanto-occipital membrane were more common in front than in rear-end collisions. Magnetic resonance image verified lesions between WAD patients and control persons, and in particular the association with head position and impact direction at time of accident, indicate that these lesions are caused by the whiplash trauma.

Whiplash trauma can damage soft tissue structures of the upper cervical spine, particularly the alar ligaments.[59–61] Whiplash trauma can damage the tectorial and posterior atlanto-occipital membranes; this can be shown on high-resolution MRI. Whiplash trauma can damage the transverse ligament. By use of high-resolution proton-weighted MR images such lesions can be detected and classified. The reliability of this classification still needs improvement.[62,63] Kinematic magnetic resonance imaging may visualize injuries of the ligaments and the joint capsules, and accompanying pathological movement patterns.[64,65]

The tectorial membrane has an essential role in maintaining upper cervical spine stability.[66] Injury to anterior spinal structures can result in clinical indications including cervical instability in extension, axial rotation, and lateral bending modes.[67] The present decreases in neck ligament strength due to whiplash provide support for the ligament-injury hypothesis of whiplash syndrome.[68]

Anterior longitudinal ligament (ALL) injuries following whiplash have been documented both in vivo and in vitro[69] and segmental hypermobility can lead to long-term instability.[67] Functional (kinematic) magnetic resonance imaging can show capsule tears and instability at the atlantoaxial joint and scar tissue around the odontoid process.[70]

2.4. Muscle

Particularly the decreased ability to relax the trapezius muscles seems to be a promising feature to identify patients with whiplash associated disorder Grade II. Assessment of the muscle dysfunction by surface electromyography offers a refinement of the whiplash associated disorder classification and provides an indication to a suitable therapeutic approach.[71] Patients with whiplash showed a distinct pattern of trigger point distribution that differed significantly from other patient groups and healthy subjects. The semispinalis capitis muscle was more frequently affected by trigger points [TrPs] in patients with whiplash.[72]

There are indications of substantial infiltration of fatty tissue into suboccipital muscles of some subjects being treated for chronic head and neck pain.[73] Fatty infiltrates in the cervical extensor musculature and widespread hyperalgesia were not features of the insidious-onset neck pain group in this study; whereas, these features have been identified in patients with chronic WAD. This novel finding may enable a better understanding of the underlying pathophysiological processes in patients with chronic whiplash.[74,75] Measuring differences in neck extensor muscle cross section area (CSA) with MRI in an asymptomatic population provides the basis for future study investigating relationships between muscular atrophy and symptoms in patients suffering from persistent neck pain.[76] Muscle atrophy could possibly account for a reduction of proprioceptive output from these muscles, and thus contribute to the perpetuation of pain.[77] Females with bilateral chronic neck pain had generalized smaller CSA of the cervical multifidus muscles compared to healthy females.[78] It seems that muscle atrophy in the rectus capitis posterior minor [RCPmin], but not in the rectus capitis posterior major [RCPmaj], was associated with suboccipital active TrPs in chronic tension-type headache, although studies with larger sample sizes are now required. It may be that nociceptive inputs in active TrPs could lead to muscle atrophy of the involved muscles. Muscle disuse or avoidance behavior can also be involved in atrophy.[79]

The same pattern of muscular reaction was found in patients with rheumatoid arthritis as in patients with soft tissue injuries of the neck [e.g., "whiplash injury"]. In the ventral muscles and the obliquus capitis inferior, the occurrence of transformations correlated strongly with the duration of symptoms; in the ventral muscles the vast majority of transformations were encountered in patients with a shorter history of symptoms, whereas in the obliquus capitis inferior the reverse occurred. In the other dorsal muscles, no correlation with the duration of symptoms was found. Muscles in which transformations had ceased, displayed on average, a significantly higher percentage of fast type-IIB fibers than were found in muscles with ongoing transformations. This strongly indicates that the transformations proceeded in the direction from "slow oxidative" to "fast glycolytic".[80]

Myofascial trigger points (MTrPs) serve to perpetuate lowered pain thresholds in uninjured tissues.[81] Active MTrPs as tonic peripheral nociceptive input contribute tremendously to the initiation and maintenance of central sensitization, to the impairment of descending inhibition.[82] MTrPs are one of the important peripheral pain generators and initiators for central sensitization.[83] Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are 2 mechanisms that could be altered by muscle pain resulting in depression of cortical outputs. There is evidence for decreased intracortical facilitation and increased short interval intracortical inhibition in response to muscle pain.[84] Surgical excision of multiple painful trigger points in the posterior neck has resulted in an increase in total active range of motion, reduced intake of pain medication, doubled the number of work hours, and generally led to a dramatic improvement in quality of life.[85]

2.5. Brain

Studies suggest different pain mechanisms in patients with chronic neck pain of non-traumatic origin compared to those with chronic neck pain due to a whiplash trauma.[86] An involvement of the posterior cingulate, parahippocampal and medial prefrontal gyri in WAD and speculate that alterations in the resting state are linked to an increased self-relevant evaluation of pain and stress.[87] Chronic pain is a common complication of traumatic brain injury[88,89] and is a significant problem in mild and moderate/severe traumatic brain injury patients.[90,91] Chronic back pain alters the human brain chemistry as the interrelationship between chemicals within and across brain regions was found to be abnormal.[92,93] A decline in gray matter volume is also found in chronic fatigue syndrome.[94] Chronic pain alters the functional connectivity of cortical regions known to be active at rest, i.e., the components of the "default mode network." These findings demonstrate that chronic pain has a widespread impact on overall brain function.[16,17] Prior research on psychosocial causes of chronic pain following whiplash are likely confounded because of a failure to account for a possible neuropathologic basis for the symptoms.[95]

2.6. Psychological

Both physical and psychological factors play a role in recovery or non-recovery from whiplash injury.[96] Psychological variables and consequences are important following whiplash in a similar manner to other types of injury.[97] Patients with whiplash-associated headache suffer psychological distress secondary to chronic pain.[98] Psychological factors are important, but not the only determinants of central hypersensitivity in whiplash patients.[99] Psychological distress resolved following a neurosurgical treatment which completely relieved pain without psychological cotherapy. The psychological distress exhibited by these patients was a consequence of the chronic somatic pain.[100] The value of the biopsychosocial model is in guiding the application of medical knowledge to the needs of each patient.[101] Trauma subjects showed hyperperfusion in right medial prefrontal cortex (mPFC)/anterior cingulate cortex and hypoperfusion in right amygdala compared with control subjects. This may underlie adaptive/recuperative processes.[102]

2.7. Temporomandibular joint

Results show that neck function is an integral part of natural jaw behavior, and that neck injury can impair jaw function and therefore disturb eating behavior.[103] These findings in the WAD group of a “faulty”, but yet consistent, jaw-neck behavior may reflect a basic importance of linked control of the jaw and neck sensory-motor systems. Neck injury is associated with deranged control of mandibular and head-neck movements during jaw opening-closing tasks, and therefore might compromise natural jaw function.[104] Observations suggest an association between neck injury and disturbed jaw function and therefore impaired eating behavior. A clinical implication is that examination of jaw function should be recommended as part of the assessment and rehabilitation of whiplash patients.[105]

2.8. Sensory motor

Patients with chronic neck pain showed altered motor control in the cervical spine.[106,107] Single trauma or cumulative microtrauma causes subfailure injuries of the ligaments and embedded mechanoreceptors. The injured mechanoreceptors generate corrupted transducer signals, which lead to corrupted muscle response pattern produced by the neuromuscular control unit. Muscle coordination and individual muscle force characteristics, i.e. onset, magnitude, and shut-off, are disrupted. This results in abnormal stresses and strains in the ligaments, mechanoreceptors and muscles, and excessive loading of the facet joints. Due to inherently poor healing of spinal ligaments, accelerated degeneration of disc and facet joints may occur. The abnormal conditions may persist, and, over time, may lead to chronic back pain via inflammation of neural tissues. The hypothesis explains many of the clinical observations and research findings about the back pain patients. The hypothesis may help in a better understanding of chronic low back and neck pain patients, and in improved clinical management.[108] Ligaments, therefore, are important structures with significant impact on motor control and a strong influence on the quality of movement, safety/stability of the joint and potential disorders that impact the safety and health of workers and athletes.[109] These subjects present either with an excess or deficit in spinal stability, which underlies their pain disorder.[110] Sensory-motor incongruence may be involved in continuing pain. Sensory disturbances including pain can be induced in the absence of nociceptive injury.

Symptoms of pain were described as numbness, pins and needles, moderate aching and/or a definite pain.[111] Ligament tension may be required to produce pain from facet joint loading. Increased allodynia after facet joint tension suggest astrocytes as a possible spinal glial mediator of such painful injury, and provide further support for facet capsule involvement in pain from mechanical neck injury.[112]

2.9. Doral root ganglion

Dorsal root ganglion [DRG] neurons can become hyperexcitable following injury. Spinal ganglia neurons are frequently related to the neurological symptoms or whiplash injury.[113] The neurons of the C5 and C6 dorsal root ganglia may have a more significant role in pain sensation of the facets than other dorsal root ganglion

neurons.[114] Integrated stress response activation, indicated by increased expression of binding protein, occurs in neurons of the DRG after painful facet distraction.[115] Results indicated potential ganglion compression in patients with a nonstenotic foramen at C5-6 and C6-7 and in patients with a stenotic foramen the injury risk greatly increases and spreads to include the C3-4 through C6-7, as well as C4-5 through C6-7 nerve roots.[116] A head-turned posture increases facet capsular ligament strain compared to a neutral head posture-a finding consistent with the greater symptom severity and duration observed in whiplash patients who have their head turned at impact.[117]

2.10. Hypothalamic-pituitary-adrenal axis

The occurrence of hypothalamic-pituitary adrenal abnormality in persons with chronic widespread pain is not fully explained by the accompanying psychological stress.[118] Dysregulation of the hypothalamic-pituitary adrenal axis in terms of reduced reactivity and enhanced negative feedback suppression exist in chronic whiplash.[119] Changes in cortical caspase levels may represent an index of cell degenerative processes leading to cognitive deficits in chronic pain states.[120]

2.11. Local nerve injuries — Injured axons and nerve endings

Traumatic injury or inflammatory irritation of the peripheral nervous system often leads to persistent pathophysiological pain states. Pain resulting from either inflammation or direct physical damage to peripheral nerve fibers and is accompanied by a pathologically increased excitability of primary sensory neurons [e.g., DRG neurons]. Following a nerve lesion, regenerative nerve sprouts grow a neuroma at the proximal nerve stump. Abnormal excitability and spontaneous discharges develop in a few days at neuroma sprouts. These tonic discharges stimulate the connecting regenerative C-fibers. After a period of longitudinal growth of regenerating nerve fibers, characteristics of the erratic impulse generator will develop. These abnormal discharges transmit impulse back to the central nervous system and presumably induce dysesthesia (abnormal perception of a sensory stimulus), such as tingling, itching or electrifying sensation, in patients with neuropathic problems. Abnormal sympathetic sprouting has been observed in a variety of animal models of pathological pain with or without damage to the peripheral axons. Sprouted fibers are found preferentially surrounding large and medium-sized sensory neurons with spontaneous activity.[121] The repetitive firing of injured neurons was facilitated at low threshold, which has been considered as a mechanism of ectopic impulse generation. At sites proximal to the nerve transection, upregulation and increased density of membrane sodium channels have been detected in injured DRG axons.[122] Six subtypes of sodium channels have been identified in DRG neurons. Some kinds of these sodium channels are sensory neuron specific and have not been found in other parts of the nervous system.[123] In these sensory neuron specific sodium channels, subtypes SNS/PN3 and SNS/NaN accrued at sites of nerve injury in neuropathic humans and animals.[124] It is known that entry of calcium ions into the nerve endings through calcium channels regulates growth-related proteins. Recently N and L-type calcium channels have been found to contribute to calcitonin gene related peptide [CGRP] release from injured nerve endings in vitro.[125] Blockade of N-, T and P type calcium channels has been found to block experimental neuropathic pain.[126,127]

Inflammation leads to sensitization of “silent” or “sleeping” nociceptors. A large group of mainly C-fibers are so-called silent nociceptors because they do not respond even to noxious mechanical stimuli of the normal joint. They begin to respond to mechanical stimulation during inflammation of the joint.[128,129] These fibers “awaken” and become much more sensitive to peripheral stimulation.[130,131] Studies have shown that sensory hypersensitivity, often in association with other prognostic indicators such as pain intensity and some psychosocial factors, is predictive of poor recovery.[132,133] Posttraumatic stress disorder hyperarousal symptoms have a detrimental influence on the recovery and severity of whiplash complaints following car accidents.[134]

2.12. Phenotype sensitization and maintained pain

Substance P and CGRP are normally expressed by nociceptor primary afferent C- and A fibers, and are implicated in sensory transmission and central sensitization. Expression of these peptides is usually down-regulated after nerve injury. Large myelinated Aβ-fibers, normally not associated with nociception, begin to express SP and CGRP after peripheral nerve injury. Therefore, low-threshold stimuli activating Aβ-fibers may lead to SP release in the dorsal horn and generate hyperexcitability that is normally driven by nociceptive inputs. A-fiber sprouting in the spinal cord is one of the central mechanisms that may also account for the development of allodynia. Peripheral nerve injury [more specifically, injury to peripheral axons of C-fibers] induces sprouting of Aβ-fiber [myelinated, low-threshold] terminals from deeper laminae [III and IV] to lamina II.[135] This rewiring may lead to the misperception of non-noxious as noxious inputs. The low-threshold stimuli activating Aβ-fibers may now cause central hyperexcitability. As a consequence, innocuous stimulation [which does not activate C-fibers or induce early-immediate response genes] causes c-fos expression within laminae I and II in the lower pain threshold state.[136] The functional phenotypic switch of rostral ventromedial medulla neurons provides a novel mechanism underlying activity-dependent plasticity and enhanced net descending inhibition after inflammation.[137] The neuroma has both afferent C-fibers and efferent post-ganglionic sympathetic C-fibers which release noradrenaline and adrenaline.

In situations of increased sympathetic activity, a raised sensitivity of the regenerating sprout towards the detection of nociceptive substances, such as bradykinin, serotonin, histamine, and capsaicin, is induced.[138] This finding shows that nociceptive receptors up-regulate at regenerating nerve terminals close to adrenoceptors. This response to sympathetic neurotransmitters may contribute to causalgia. The influence of sympathetic nervous injury goes far beyond the peripheral responsiveness of sympathetic–afferent interactions. The excitatory effects on nociceptive receptors of the sympathetic nervous system are also caused by hypophysical-adrenocortical system, neuroimmune interactions, neuropeptides, chronic inflammation, psychosomatically mediated mental, and emotional reactions.[139] Nociceptive-specific cells are mostly found superficially and synapse with Aδ-and C-fibers only. These cells fire action potentials when a painful stimulus is detected at the periphery. Cells which receive input exclusively from Aβ-fibers are proprioceptive and only respond to touch. A third type of neuron, termed wide dynamic range [WDRs], receives input from all three types of sensory fibers, and therefore respond to the full range of stimulation, from light touch to noxious pinch, heat, and chemicals. These neurons fire action potentials in a graded fashion depending on stimulus intensity, and also exhibit “wind-up”, a short-lasting form of synaptic plasticity. During wind-up, repetitive stimulation of WDR neurons induces an increase of their evoked response and postdischarge with each stimulus.[140] Most nociceptive Aδ-and C-fibers terminate superficially in laminae I–II,

with a smaller number reaching deeper laminae, whereas Aβ-fibers predominantly innervate laminae III–VI.[141] Fig. 1

2.13. Cytokines/chemokines in neuropathic pain

The central and peripheral changes of underlying cytokines may play important roles in the mechanism of neuropathic pain. Cytokines are a category of signaling proteins and glycoproteins that, like hormones and neurotransmitters, are used extensively in cellular communication. Cytokines have been variously named as lymphokines, interleukins, and chemokines. The first chemokine to be implicated in pain was CXCL8 [also named IL-8], which is released by activated macrophages and endothelial cells. Growing evidence indicates that proinflammatory cytokines, such as IL-1beta, IL-6, and TNF-alpha, are induced in the spinal cord under various injury conditions and contribute to pain hypersensitivity.[143] Recently researchers have focused on the roles of IL-1 and TNF-α.[144,145]

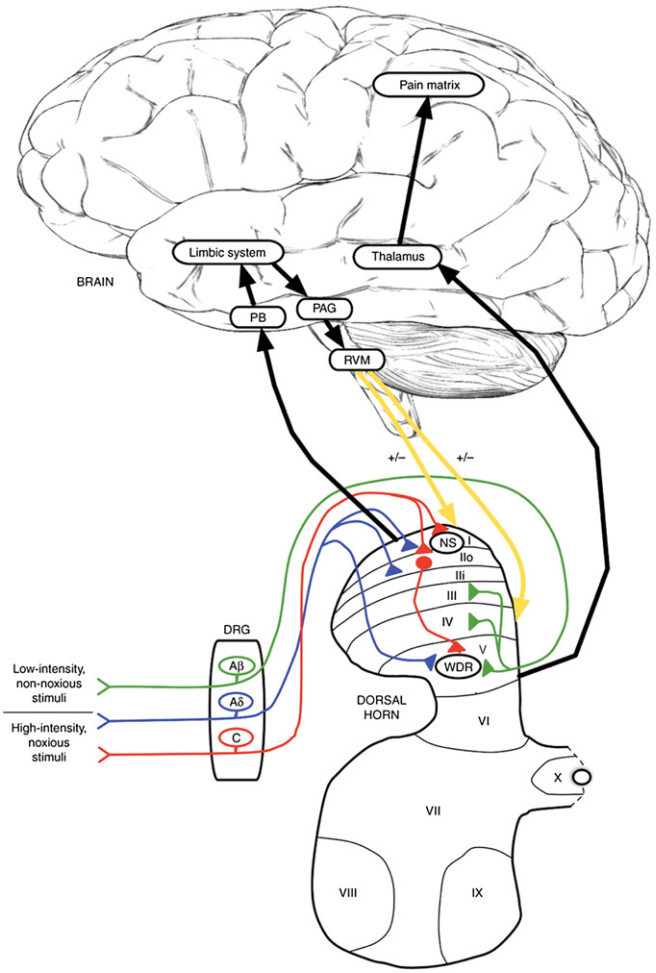

Fig. 1. Pain pathways from periphery to brain. Primary afferent fibers (Ab-, Ad-, and C-fibers) transmit impulses from the periphery, through the dorsal root ganglion (DRG) and into the dorsal horn of the spinal cord. Nociceptive specific (NS) cells are mainly found in the superficial dorsal horn (laminae I–II), whereas most wide dynamic ranges (WDRs) are located deeper (lamina V). Projection neurons from lamina I innervate areas such as the parabrachial area (PB) and periaqueductal grey (PAG) and such pathways are affected by limbic areas. From here descending pathways (yellow arrows) from brainstem nuclei such as the rostral ventromedial medulla (RVM) are activated and modulate spinal processing. Lamina V neurons mainly project to the thalamus (spinothalamic tract), and from here the various cortical regions forming the "pain matrix" (primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices) are activated.[142]

Inflammatory hyperalgesia has been prevented by experimental administration of endogenous IL-1 receptor antagonist.[146] Neutralizing antibodies to IL-1 receptors reduced pain-associated behavior in mice with experimental neuropathy.[147] Combined epineurial therapy with neutralizing antibodies to TNF-and IL-1 receptors had additive effects in reducing neuropathic pain.

Nerve biopsies from patients with neuropathies revealed higher TNF-immunoreactivities in myelinating Schwann cells when the neuropathy was painful, and serum soluble TNF-α-receptor 1 levels were higher in patients with central-mediated allodynia.[148] Involvement of TNF-alpha has been demonstrated with the upstream cascade of cellular events that may involve the underlying pathogenesis of neuropathic pain.[149] Nerve growth factor causes acute sensitization of sensory neurons through a number of signaling cascades and that it also can increase expression and trafficking of molecules that mediate excitability of sensory neurons.[150]

2.14. Central sensitization and plasticity

Healthy nerve terminals uptake signal substances, including NGF and other growth factors from their target cells, are transmitted by axonal transport to the DRG.[151] After nerve injury, sprouts can no longer take up these growth factors to the DRG neurons.[152] The gene transcription and protein synthesis are altered. At the level of transcription control in the DRG neurons, the c-jun gene [an oncoprotein-involved in the regulation or synthesis of proteins] can be inducted one day after axotomy.[153] The c-Jun expression in the DRG neurons after nerve transection are associated with changes in neuropeptide levels: SP and CGRP decrease, and galanin and nitric oxide synthase increase dramatically during the weeks and months following axotomy.[154] The increased release and production of nitric oxide synthase at the intraspinal presynaptic terminal may facilitate afferent synaptic transmission to the dorsal horn neurons. Therefore, the pathophysiological processes following nerve injury are carried from the peripheral to the central nervous system.[155] This phenomenon may contribute to spinal neuronal sensitization and hyperalgesia.

Repetitive noxious stimulation leads to the increased activities of aspartate and glutamate at N-methyl-D-aspartate and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionicacid [AMPA]/kainite receptors, which produce an influx of extracellular $Ca2+$ and activation of protein kinase C [PKC] in dorsal horn neurons.[156] The increased intracellular $Ca2+$ induces the expression of c-fos [a cellular proto-oncogene belonging to the immediate early gene family of transcription factors].[157]

Noxious stimulation can induce c-fos expression in dorsal horn neurons [mainly in laminae I and II], which may relate to prolonged functional and adaptive responses in the spinal cord. Fos protein is believed to be involved in the transcriptional control of genes that encode a variety of neuropeptides, including enkephalin and dynorphin. Enkephalin typically produces antinociceptive effects.

Dynorphin [dynorphin is an opioid peptide with high selectivity for the kappa-opioid receptor subtype] has direct excitatory effects on spinal projection neurons and may also produce inhibition via a negative feedback mechanism on dynorphin containing neurons.[158] Elevated levels of the opioid dynorphin can unexpectedly activate bradykinin receptors, contributing to the maintenance of neuropathic pain.[159] The end-effect of these changes may have complex modulations in the development of central plasticity.[160] Electrophysiologically, there is plenty evidence for sensitization of dorsal horn cells and enhancement of spinal reflexes by a repetitive or prolonged noxious stimulation. This enhanced synaptic transmission is manifested by long-term potentiation [LTP] following a short train of stimulation at C-fiber.[160] The transition of LTP

between spinal interneurons involves glutamate and neurokinin 1 receptors. Blocking the LTP spreading with the N-methyl-D-aspartate and/or neurokinin 1 receptor antagonists may be a potential treatment of neuropathic pain.[161]

Gamma-aminobutyric acid [GABA] is an amino acid and inhibitory neurotransmitter in the central nervous system. Partial nerve injury also induces GABAergic inhibitory interneuron apoptosis [a form of programmed cell death] and reduces inhibition in the superficial dorsal horn. This transynaptic neural degeneration also contributes to abnormal pain sensitivity.[162]

At the peripheral level, a nerve lesion may induce loss of normal electrical insulation in the afferent fibers, which makes these neurons more accessible to diffusible substances and may trigger the production of alpha adrenoceptors on the membrane of primary afferent neurons. In this condition, noradrenaline released by sympathetic terminals as well as circulating catecholamines released by the adrenal glands can evoke pain by producing excitation of a number nociceptors and/or enhancing their responsiveness to nociceptive stimuli. The injured fibers may develop abnormal electrogenic membrane properties that accompany the loss of normal electric insulation. This may lead to nonsynaptic communication between different classes of neurons ["ephaptic transmission", i.e., a type of electric coupling between contiguous neurons entailing a direct transfer of current].[163]

Regeneration after nerve injury results in the formation of neuromas[164,165] and sprouting of new nerve projections among uninjured neighboring neurons.[166] Collateral sprouting then leads to altered sensory properties that may be realized as expanded receptive fields. Uncontrolled neuronal firing after experimental nerve injury is largely attributed to increased expression of sodium channels. This mechanism is supported by several lines of evidence, including blockade of neuropathic pain with sodium-channel–blocking local anesthetics.[167] Demyelination of diseased nerves may be another cause of increased neuronal excitability.[168]

Subfailure loading conditions are associated with altered joint mechanics and collagen fiber disorganization and imply ligament damage. Substructural damage in the facet capsule has the potential to both directly modulate nerve fiber signaling and produce sustained physiologic modifications that may initiate persistent pain.[169] Inflammatory agents released from [or recruited by] nucleus pulposus affect the DRG [and/or are transported to cord] to enhance primary afferent excitation of nociceptive dorsal horn neurons. The normally non-noxious stimulus is inducing dorsal horn neuronal wind-up that is interpreted as pain and further enhances the dorsal spinal neuronal excitability to subsequent sensory input.[170,171]

2.15. Deep tissue pain

A whiplash type injury occurs in deep tissue that may involve the facets, disc, ligaments, or muscles.[19] Deep tissue pain is different from superficial pain; the former lasts longer than the latter[172,173] and does not follow dermatomal patterns.[174,175] The distributions and interconnections of hypothalamic and midbrain neurons activated by superficial and deep nociceptors, and by C- compared with Aδ-nociceptors, have revealed neuronal circuitry that can distinguish between escapable [superficial] and inescapable [deep] pain.[176]

2.16. Referred pain

The classical studies by Lewis and Kellgren[177] showed that local injections of hypertonic saline into interspinous ligaments produced hyperalgesia and referred pain elsewhere and does not follow dermatomal patterns and later by Feinstein et al.[178] with paravertebral injections. Whiplash pain may be referred from the zygapophysial [facet] joints and discs. Cervical zygapophysial joint pain is common among patients with chronic neck pain after whiplash.[175,179–181] The prevalence of chronic cervical zygapophysial joint pain [C2-C3 or below] was 60 percent [95 percent confidence interval, 46 percent, 73 percent].[182] Cervical internal disc disruption can elicit axial and peripheral symptoms[183] and lumbar disc stimulation may produce pain that extends to below the knee.[184]

Early mechano-sensitization after an acute whiplash injury can lead to the development of further sensitization in patients with long-term disability.[185] The semispinalis capitis muscle was more frequently affected by trigger points in patients with whiplash, whereas other neck and shoulder muscles and the masseter muscle did not differentiate between patients with whiplash and patients with non-traumatic chronic cervical syndrome or fibromyalgia.[186] Active trigger points are more likely to occur in certain muscles in the presence of cervical disc lesions at specific levels.[72]

2.17. Widespread pain

Different mechanisms underlie hyperalgesia localized at areas surrounding the site of pain and hyperalgesia generalized to distant body areas. Central hypersensitivity as a determinant of neck pain is probably a dynamic condition that is influenced by the presence and activity of a nociceptive focus.[187] Fibromyalgia syndrome (FMS) is characterized by widespread pain, fatigue, sleep abnormalities, and distress. Wind-up and central sensitization, which rely on central pain mechanisms, occur after prolonged C-nociceptor input and depend on activation of nociceptor specific neurons and wide dynamic range neurons in the dorsal horn of the spinal cord. Thalamic activity, which contributes significantly to pain processing, was decreased in fibromyalgia.[188] One study indicated that FMS was 13 times more frequent following neck injury than following lower extremity injury. All patients continued to be employed, and insurance claims were not increased in patients with FMS.[189] In patients with chronic pain after whiplash injury and in fibromyalgia patients there can be spinal cord hyperexcitability. This can cause exaggerated pain following low intensity nociceptive or innocuous peripheral stimulation Patients with chronic pain after whiplash injury and fibromyalgia patients display exaggerated pain after sensory stimulation.[190]

2.18. Genetics

Genetics are involved in synaptic transmission, conduction, transduction, and modulation.[191] As the greater the quantity of opioid receptors one has, the more likely it is that the result will be less perception of pain. Some patients may be genetically predisposed to decreased amounts of opioid receptors.[192] Catecholamine-O-methyltransferase (COMT) an enzyme that metabolizes neurotransmitters such as epinephrine, norepinephrine and dopamine and that has been implicated in the modulation of persistent pain, as well as cognition and mood activity. COMT activity substantially influences pain sensitivity, and the three major haplotypes determine COMT activity in humans that inversely correlates with pain sensitivity.[193] The presence or absence of a COMT pain vulnerable genotype was more predictive of moderate or severe acute neck pain than the crash related characteristics assessed, including rear-end collision type, airbag deployment, and whether or not the car was drivable at the scene.[194] TWIK-related spinal cord potassium channel (TRESK, encoded by KCNK18) has a role in migraine headache sufferers.[195]

3. Conclusion

There are some that doubt the validity of the chronic whiplash syndrome.[196] Two studies conducted in Lithuania[197,198] are often used to argue that cultural expectations, and factors related to compensation and litigation, affect the reporting and treatment of whiplash symptoms. The Lithuanian studies recruited subjects from the police station in a former Soviet-controlled country and looked for people who would complain 1–3 years after a collision. Eighty-five percent of the participants in these studies were men. Most studies indicate there are a greater number of women with chronic complaints. The first Lithuanian study by Schrader et al[197] comprised 202 individuals who had been involved in motor vehicle crashes. The total study cohort needed to be at least 3000 in order to have sufficient statistical power to discern a significant difference between the two groups.[199] In the second Lithuanian study,[198] the control group was worse off than the whiplash group.

Limitations are that pain is complex and experiments on mechanisms of pain are other than human studies. Animal studies may not be conclusive for answers involving humans but can give some insights into mechanisms.[200] Neck and back injury is independent of crash severity and may occur at low speeds.[2–6] Nociceptive pain is physiological pain produced by noxious stimuli that activate high-threshold nociceptor neurons and is a stimulus-dependent pain.[201] Inflammatory pain occurs in response to tissue injury and the subsequent inflammatory response. To aid healing and repair of the injured body part, the sensory nervous system undergoes a profound change in its responsiveness as normally innocuous stimuli now produce pain and responses to noxious stimuli are both exaggerated and prolonged.[202]

Dysfunctional pain is an amplification of nociceptive signaling in the absence of either inflammation or neural lesions. There may be no known structural nervous system lesion or active peripheral inflammation. It may be present with lack of stimulus.[203] Neuropathic pain is maladaptive plasticity caused by a lesion or disease affecting the somatosensory system, alters nociceptive signal processing so that pain is felt in the absence of a stimulus, and responses to innocuous and noxious stimuli are enhanced. There may be a marked neuroimmune response.[204,205] Damage to the peripheral nervous system often leads to chronic neuropathic pain characterized by spontaneous pain and an exaggerated response to painful and/or innocuous stimuli. This pain condition is extremely debilitating and usually difficult to treat.[204] Sensory hypoesthesia and hypersensitivity co-exist in the chronic whiplash condition. Peripheral afferent nerve fiber involvement could be a further manifestation of disordered central pain processing.[206] With mechanical allodynia, a pain threshold/detection threshold of less than 2.0 suggests that altered central nervous system processing of Aβ input contributing to allodynia.[206,207]

Chronic cervical radiculopathy (grade III WAD) and grade II WAD are both characterized by widespread sensory hypersensitivity that likely reflects altered central pain processing mechanisms.[208] Sensory hypoesthesia while present in chronic whiplash is not a feature of chronic idiopathic neck pain. These findings indicate that different pain processing mechanisms underlie these two neck pain conditions and may have implications for their management.[209] Sensory hypoesthetic disturbances persisted in those who reported higher levels of pain and disability and sensory hypersensitivity soon after the injury. These findings indicate the involvement of the central inhibitory mechanisms after whiplash injury and the potential role of continuous nociceptive input in sustaining such phenomena.[210]

Peripheral nerve injury is followed by change in expression of neurotransmitters, neuromodulators, growth factors and neuroactive molecules in primary afferent neurons located in dorsal root ganglion of the spinal cord. These changes in-turn induce sensitization of primary afferents inputs (peripheral sensitization) leading to exaggerated pain perception in an injured tissue or territory innervated by an injured nerve.[211] Central sensitization encompasses increased activity of pain facilitatory pathways, temporal summation of second pain or wind-up,[212,213] malfunctioning of descending antinociceptive mechanisms,[214] altered sensory processing in the brain, and long-term potentiation of neuronal synapses in several brain areas, including the anterior cingulate cortex.[215]

Muscle fatty infiltrates in the cervical extensors occur soon following whiplash injury and suggest the possibility for the occurrence of a more severe injury with subsequent posttraumatic stress disorder in patients with persistent symptoms.[216]

Assessment of whiplash injured patients may need proper imaging and to include more detailed sensory testing using quantitative sensory testing.[15,217] Whiplash is a heterogeneous condition with some individuals showing features suggestive of neuropathic pain. Those with injury to the discs, facets, or upper cervical ligaments will not improve spontaneously will have chronic symptoms.[218] Those with other than a nociceptive type of pain may be more difficult to treat. A predominantly neuropathic pain component is related to a complex presentation of sensory hypersensitivity and higher pain/disability.[26]

Conflict of interest

None.

References

1. Turk DC, Okifuji A. Pain terms and taxonomies. In: Loeser JD, Butler SH, Chapman CR, Turk DC, editors. *Bonica's management of pain*. 3 ed. Lippincott Williams & Wilkins; 2001. p. 18–25.
2. Bartsch AJ, Gilbertson LG, Prakash V, Morr DR, Wiechel JF. Minor crashes and "whiplash" in the United States. 52nd AAAM Annual Conference. *Ann Adv Automotive Med* 2008:117–30.
3. Krafft M, Kullgren A, Ydenius A, et al. *Rear impact neck protection by reducing occupant forward acceleration a study of cars on Swedish roads equipped with crash recorders and a new anti-whiplash device*. Proceedings of the International IRCOBI Conference. Graz, Austria 2004. p. 221–31.
4. Beattie N, Lovell ME. Can patients with low energy whiplash associated disorder develop low back pain? *Injury* 2009 Jul 20.
5. Croft AC, Freeman MD. Correlating crash severity with injury risk, injury severity, and long-term symptoms in low velocity motor vehicle collisions. *Med Sci Monit* 2005 Oct;**11**(10):RA316–21.
6. Jackson R. The positive findings in alleged neck injuries. *Am J Orthop* 1964 Aug-Sep;**6**:178–87.
7. Julius D, Basbaum AI. Molecular mechanism of nociception. *Nature* 2001;**413**:203–10.
8. Julius D, McClesky EW. Cellular and molecular properties of primary afferent neurons. In: McMahon S, Kolzenburg M, editors. *Wall and Melzack"s textbook of pain*. 5th ed. Philadelphia: Elsevier/Churchill Livingstone; 2006.
9. Meyer RA, Ringkamp M, Campbell JN, Raja SN. Peripherial mechanisms of cutaneous nociception. In: McMahon S, Kolzenburg M, editors. *Wall and Mexzack"s textbook of pain*. 5th ed. Philadelphia: Elsevier/Churchill Livingstone; 2006.
10. Sterling M, Treleaven J, Jull G. Responses to a clinical test of mechanical provocation of nerve tissue in whiplash associated disorder. *Man Ther* 2002;**7**:89–94.
11. Moog M, Quintner J, Hall Y, Zusman M. The late whiplash syndrome: a psychophysical study. *Eur J Pain* 2002;**6**:283–94.
12. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury is associated with poor recovery. *Pain* 2003;**104**:509–17.
13. Sterling M. A proposal new classification system for whiplash associated disorders –implications for assessment and management. *Man Ther* 2004;**9**:60–70.
14. Sterling M, Jull G, Vicenzino B, Kenardy J. Characterization of acute whiplash-associated disorders. *Spine* 2004;**29**:182–8.
15. Curatolo M, Peterson-Felix S, Arendt-Nielsen L, Giani C, Abinden AM, Radanov BP. Central hypersensitivity in chronic pain after whiplash injury. *Clin J Pain* 2001;**17**:306–15.
16. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J Neurosci* 2008 Feb 6;**28**(6):1398–403.

17. Mantini D, Caulo M, Ferretti A, Romani GL, Tartaro A. Noxious somatosensory stimulation affects the default mode of brain function: evidence from functional MR imaging. *Radiology* 2009 Dec;**253**(3):797–804.
18. Freeman MD, Rosa S, Harshfield D, Smith F, Bennett R, Centeno CJ, et al. A case-control study of cerebellar tonsillar ectopia (Chiari) and head/neck trauma (whiplash). *Brain Inj* 2010;**24**(7–8):988–94.
19. Malanga GA, editor. *Cervical flexion-extension/whiplash injuries. Spine: state of the art reviews*. Philadelphia: Hanley & Belfus; 1998.
20. Siegmund GP, Myers BS, Davis MB, Bohnet HF, Winkelstein BA. Human cervical motion segment flexibility and facet capsular ligament strain under combined posterior shear, extension and axial compression. *Stapp Car Crash J* 2000 Nov;**44**:159–70.
21. Pearson AM, Ivancic PC, Ito S, Panjabi MM. Facet joint kinematics and injury mechanisms during simulated whiplash. *Spine* 2004;**29**:390–7.
22. Cusick JF, Pintar FA, Yoganandan N. Whiplash syndrome: kinematic factors influencing pain patterns. *Spine* 2001 Jun 1;**26**(11):1252–8.
23. Lee KE, Davis MB, Mejilla RM, Winkelstein BA. In vivo cervical facet capsule distraction: mechanical implications for whiplash and neck pain. *Stapp Car Crash J* 2004 Nov;**48**:373–95.
24. Lu Y, Chen C, Kallakuri S, Patwardhan A, Cavanaugh JM. Neural response of cervical facet joint capsule to stretch: a study of whiplash pain mechanism. *Stapp Car Crash J* 2005 Nov;**49**:49–65.
25. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci* 2009;**32**:1–32.
26. Sterling M, Pedler A. A neuropathic pain component is common in acute whiplash and associated with a more complex clinical presentation. *Man Ther* 2009 Apr;**14**(2):173–9.
27. Freynhagen R, Baron R. The evaluation of neuropathic components in low back pain. *Curr Pain Headache Rep* 2009 Jun;**13**(3):185–90.
28. Seifert F, Maihöfner C. Central mechanisms of experimental and chronic neuropathic pain: findings from functional imaging studies. *Cell Mol Life Sci* 2009 Feb;**66**(3):375–90.
29. Quinn KP, Winkelstein BA. Cervical facet capsular ligament yield defines the threshold for injury and persistent joint-mediated neck pain. *J Biomech* 2007;**40**(10):2299–306.
30. Kallakuri S, Singh A, Lu Y, Chen C, Patwardhan A, Cavanaugh JM. Tensile stretching of cervical facet joint capsule and related axonal changes. *Eur Spine J* 2008 Apr;**17**(4):556–63.
31. Cavanaugh J. Neural mechanisms of lumbar pain. *Spine* 1995;**20**:1804–9.
32. Garfin S, Rydevik B, Brown R. Compressive neuropathy of spinal nerve roots: a mechanical or biological problem? *Spine* 1991;**16**:162–6.
33. Garfin S, Rydevik B, Lind B, Massie J. Spinal nerve root compression. *Spine* 1995;**20**:1810–20.
34. Murata Y, Rydevik B, Takahashi K, Larsson K, Olmarker K. Incision of the intervertebral disc induces disintegration and increases permeability of the dorsal root ganglion capsule. *Spine* 2005;**30**:1712–6.
35. Takahashi N, Yabuki S, Aoki Y, Kikuchi S. Pathomechanisms of nerve root injury caused by disc herniation: an experimental study of mechanical compression and chemical irritation. *Spine* 2003;**8**:435–41.
36. Takebayashi T, Cavanaugh J, Ozaktay A, Kallakuri S, Chen C. Effect of nucleus pulposus on the neural activity of dorsal root ganglion. *Spine* 2001;**26**:940–5.
37. Igarashi A, Kikuchi S, Konno S, Olmarker K. Inflammatory cytokines released from the facet joint tissue in degenerative lumbar spinal disorders. *Spine* 2004 Oct 1;**29**(19):2091–5.
38. Igarashi A, Kikuchi S, Konno S. Correlation between inflammatory cytokines released from the lumbar facet joint tissue and symptoms in degenerative lumbar spinal disorders. *J Orthop Sci* 2007 Mar;**12**(2):154–60.
39. Ahn SH, Cho YW, Ahn MW, Jang SH, Sohn YK, Kim HS. mRNA expression of cytokines and chemokines in herniated lumbar intervertebral discs. *Spine* 2002 May 1;**27**(9):911–7.
40. Burke JG, Watson RW, McCormack D, Dowling FE, Walsh MG, Fitzpatrick JM. Intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators. *J Bone Jt Surg Br* 2002 Mar;**84**(2):196–201.
41. Kang JD, Georgescu HI, McIntyre-Larkin L, Stefanovic-Racic M, Evans CH. Herniated cervical intervertebral discs spontaneously produce matrix metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2. *Spine* 1995 Nov 15;**20**(22):2373–8.
42. Taiwo YO, Levine JD. Prostaglandins inhibit endogenous pain control mechanisms by blocking transmission at spinal noradrenergic synapses. *J Neurosci* 1988 Apr;**8**(4):1346–9.
43. Ito S, Ivancic PC, Panjabi MM, Cunningham BW. Soft-tissue injury threshold during simulated whiplash: a biomechanical investigation. *Spine* 2004;**29**:979–87.
44. Miyazaki M, Hymanson HJ, Morishita Y, He W, Zhang H, Wu G, et al. Kinematic analysis of the relationship between sagittal alignment and disc degeneration in the cervical spine. *Spine (Phila Pa 1976)* 2008 Nov 1;**33**(23):E870–6.
45. Miyazaki M, Hong SW, Yoon SH, Zou J, Tow B, Alanay A, et al. Kinematic analysis of the relationship between the grade of disc degeneration and motion unit of the cervical spine. *Spine (Phila Pa 1976)* 2008 Jan 15;**33**(2):187–93.
46. MacNab I. Acceleration injuries of the cervical spine. *J Bone Jt Surg* 1964;**46A**:1797–9.
47. Ommaya AK, Faas F, Yarnell P. Whiplash injury and brain damage — an experimental study. *JAMA* 1968;**204**:285–9.
48. Taylor JR, Kakulas BA. Neck injuries. *Lancet* 1991;**338**:1343.
49. Lord SM, Barnsley L, Wallis BJ, Bogduk N. Chronic cervical zygapophyseal joint pain after whiplash. A placebo-controlled prevalence study. *Spine* 1996;**21**:1737–45.
50. Giles LGF, Harvey AR. Immunohistochemical demonstration of nociceptors in the capsule and synovial folds of human zygapophyseal joints. *Br J Rheumatol* 1987;**26**:362–4.
51. Inami S, Shiga T, Tsujino A, Yabuki T, Okado N, Ochiai N. Immunohistochemical demonstration of nerve fibers in the synovial fold of the human cervical facet joint. *J Orthop Res* 2001 Jul;**19**(4):593–6.
52. Taylor JR, Finch P. Acute injury of the neck: anatomical and pathological basis of pain. *Ann Acad Med Singapore* 1993 Mar;**22**(2):187–92.
53. Brisby H. Pathology and possible mechanisms of nervous system response to disc degeneration. *J Bone Jt Surg Am* 2006 Apr;**88**(2):68–71.
54. Anderson AV. Cervicogenic processes: results of injury to the cervical spine. *Pain Pract* 2001;**11**:9–11.
55. Cavanaugh JM, Lu Y, Chen C, Kallakuri S. Pain generation in lumbar and cervical facet joints. *J Bone Jt Surg Am* 2006 Apr;**88**(2):63–7.
56. Kallakuri S, Singh A, Chen C, Cavanaugh JM. Demonstration of substance P, calcitonin gene related peptide, and protein gene product 9.5 containing nerve fibers in human cervical facet joint capsules. *Spine* 2004 Jun 1;**29**(11):1182–6.
57. Jonsson Jr H, Bring G, Rauschning W, Sahlstedt B. Hidden cervical spine injuries in traffic accident victims with skull fractures. *J Spinal Disord* 1991;**4**:251–63.
58. Pettersson K, Hildingsson C, Toolanen G, Fagerlund M, Bjornebrink J. Disc pathology after whiplash injury. A prospective magnetic resonance imaging and clinical investigation. *Spine* 1997;**22**:283–7. discussion 288.
59. Kaale BR, Krakenes J, Albrektsen G, Wester K. Whiplash-associated disorders impairment rating: neck disability index score according to severity of MRI findings of ligaments and membranes in the upper cervical spine. *J Neurotrauma* 2005 Apr;**22**(4):466–75.
60. Kaale BR, Krakenes J, Albrektsen G, Wester K. Head position and impact direction in whiplash injuries: associations with MRI-verified lesions of ligaments and membranes in the upper cervical spine. *J Neurotrauma* 2005 Nov;**22**(11):1294–302.
61. Krakenes J, Kaale BR. Magnetic resonance imaging assessment of craniovertebral ligaments and membranes after whiplash trauma. *Spine* 2006 Nov 15;**31**(24):2820–6.
62. Krakenes J, Kaale BR, Moen G, Nordli H, Gilhus NE, Rorvik J. MRI of the tectorial and posterior atlanto-occipital membranes in the late stage of whiplash injury. *Neuroradiology* 2003 Sep;**45**(9):585–91.
63. Krakenes J, Kaale BR, Nordli H, Moen G, Rorvik J, Gilhus NE. MR analysis of the transverse ligament in the late stage of whiplash injury. *Acta Radiol* 2003 Nov;**44**(6):637–44.
64. Lindgren KA, Kettunen JA, Paatelma M, Mikkonen RH. Dynamic kine magnetic resonance imaging in whiplash patients and in age- and sex-matched controls. *Pain Res Manag* 2009 Nov- Dec;**14**(6):427–32.
65. Johansson BH. Whiplash injuries can be visible by functional magnetic resonance imaging. *Pain Res Manag* 2006;**11**(3):197–9. Autumn.
66. Harris MB, Duval MJ, Davis Jr JA, Bernini PM. Anatomical and roentgenographic features of atlantooccipital instability. *J Spinal Disord* 1993 Feb;**6**(1):5–10.
67. Stemper BD, Yoganandan N, Pintar FA, Rao RD. Anterior longitudinal ligament injuries in whiplash may lead to cervical instability. *Med Eng Phys* 2006 Jul;**28**(6):515–24.
68. Tominaga Y, Ndu AB, Coe MP, Valenson AJ, Ivancic PC, Ito S, et al. Neck ligament strength is decreased following whiplash trauma. *BMC Musculoskelet Disord* 2006 Dec 21;**7**:103.
69. Ivancic PC, Pearson AM, Panjabi MM, Ito S. Injury of the anterior longitudinal ligament during whiplash simulation. *Eur Spine J* 2004 Feb;**13**(1):61–8.
70. Johansson BH. Whiplash injuries can be visible at surgery. *Pain Res Manage* 2006;**11**(3):197–9.
71. Nederhand MJ, IJzerman MJ, Hermens HJ, Baten CT, Zilvold G. Cervical muscle dysfunction in the chronic whiplash associated disorder grade II (WAD-II). *Spine* 2000 Aug 1;**25**(15):1938–43.
72. Ettlin T, Schuster C, Stoffel R, Brüderlin A, Kischka U. A distinct pattern of myofascial findings in patients after whiplash injury. *Arch Phys Med Rehabil* 2008 Jul;**89**(7):1290–3.
73. Hallgren RC, Greenman PE, Rechtien JJ. Atrophy of suboccipital muscles in patients with chronic pain: a pilot study. *J Am Osteopath Assoc* 1994 Dec;**94**(12):1032–8.
74. Elliott J, Sterling M, Noteboom JT, Darnell R, Galloway G, Jull G. Fatty infiltrate in the cervical extensor muscles is not a feature of chronic, insidious-onset neck pain. *Clin Radiol* 2008 Jun;**63**(6):681–7.
75. Elliott J, Jull G, Noteboom JT, Galloway G. MRI study of the cross-sectional area for the cervical extensor musculature in patients with persistent whiplash associated disorders (WAD). *Man Ther* 2008 Jun;**13**(3):258–65.
76. Elliott JM, Jull GA, Noteboom JT, Durbridge GL, Gibbon WW. Magnetic resonance imaging study of cross-sectional area of the cervical extensor musculature in an asymptomatic cohort. *Clin Anat* 2007 Jan;**20**(1):35–40.
77. Fernández-de-Las-Peñas C, Bueno A, Ferrando J, Elliott JM, Cuadrado ML, Pareja JA. Magnetic resonance imaging study of the morphometry of cervical extensor muscles in chronic tension-type headache. *Cephalalgia* 2007 Apr;**27**(4):355–62.

78. Fernández-de-las-Peñas C, Albert-Sanchís JC, Buil M, Benitez JC, Alburquerque-Sendín F. Cross sectional area of cervical multifidus muscle in females with chronic bilateral neck pain compared to controls. *J Orthop Sports Phys Ther* 2008 Apr;**38**(4):175–80.
79. Fernández-de-Las-Peñas C, Cuadrado ML, Arendt-Nielsen L, Ge HY, Pareja JA. Association of cross sectional area of the rectus capitis posterior minor muscle with active trigger points in chronic tension type headache: a pilot study. *Am J Phys Med Rehabil* 2008 Mar;**87**(3):197–203.
80. Uhlig Y, Weber BR, Grob D, Müntener M. Fiber composition and fiber transformations in neck muscles of patients with dysfunction of the cervical spine. *J Orthop Res* 1995 Mar;**13**(2):240–9.
81. Freeman MD, Nystrom A, Centeno C. Chronic whiplash and central sensitization; an evaluation of the role of a myofascial trigger points in pain modulation. *J Brachial Plex Peripher Nerve Inj* 2009 Apr 23;**4**:2.
82. Ge HY. Prevalence of myofascial trigger points in fibromyalgia: the overlap of two common problems. *Curr Pain Headache Rep* 2010 Oct;**14**(5):339–45.
83. Xu YM, Ge HY, Arendt-Nielsen L. Sustained nociceptive mechanical stimulation of latent myofascial trigger point induces central sensitization in healthy subjects. *J Pain* 2010 Dec;**11**(12):1348–55.
84. Schabrun SM, Hodges PW. Muscle pain differentially modulates short interval intracortical inhibition and intracortical facilitation in primary motor cortex. *J Pain* 2012 Feb;**13**(2):187–94.
85. Duffy MF, Stuberg W, DeJong S, Gold KV, Nystrom NA. Case report: whiplash-associated disorder from a low-velocity bumper car collision: history, evaluation, and surgery. *Spine (Phila Pa 1976)* 2004 Sep 1;**29**(17):1881–4.
86. Sundström T, Guez M, Hildingsson C, Toolanen G, Nyberg L, Riklund K. Altered cerebral blood flow in chronic neck pain patients but not in whiplash patients: a 99mTc-HMPAO rCBF study. *Eur Spine J* 2006 Aug;**15**(8):1189–95.
87. Linnman C, Appel L, Söderlund A, Frans O, Engler H, Furmark T, et al. Chronic whiplash symptoms are related to altered regional cerebral blood flow in the resting state. *Eur J Pain* 2009 Jan;**13**(1):65–70.
88. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA* 2008 Aug 13;**300**(6):711–9.
89. Smith-Seemiller L, Fow NR, Kant R, Franzen MD. Presence of post-concussion syndrome symptoms in patients with chronic pain vs mild traumatic brain injury. *Brain Inj* 2003;**17**(3):199–206.
90. Uomoto JM, Esselman PC. Traumatic brain injury and chronic pain: differential types and rates by head injury severity. *Arch Phys Med Rehabil* 1993 Jan;**74**(1):61–4.
91. Lahz S, Bryant RA. Incidence of chronic pain following traumatic brain injury. *Arch Phys Med Rehabil* 1996 Sep;**77**(9):889–91.
92. Grachev ID, Fredrickson BE, Apkarian AV. Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. *Pain* 2000 Dec 15;**89**(1):7–18.
93. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 2004 Nov 17;**24**(46):10410–5.
94. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage* 2005 Jul 1;**26**(3):777–81.
95. Freeman MD, Rosa S, Harshfield D, Smith F, Bennett R, Centeno CJ, Kornel E, Nystrom A, Heffez D, Kohles SS. A case-control study of cerebellar tonsillar ectopia (Chiari) and head/neck trauma (whiplash). *Brain Inj* 2010;**24**(7–8):988–94.
96. Sterling M, Jull G, Vicenzino B, Kenardy J, Darnell R. Physical and psychological factors predict outcome following whiplash injury. *Pain* 2005 Mar;**114**(1–2):141–8.
97. Mayou R, Bryant B. Psychiatry of whiplash neck injury. *Br J Psychiatry* 2002 May;**180**:441–8.
98. Wallis BJ, Lord SM, Barnsley L, Bogduk N. The psychological profiles of patients with whiplash associated headache. *Cephalalgia* 1998 Mar;**18**(2):101–5. discussion 72–73.
99. Sterling M, Hodkinson E, Pettiford C, Souvlis T, Curatolo M. Psychologic factors are related to some sensory pain thresholds but not nociceptive flexion reflex threshold in chronic whiplash. *Clin J Pain* 2008 Feb;**24**(2):124–30.
100. Wallis BJ, Lord SM, Bogduk N. Resolution of psychological distress of whiplash patients following treatment by radiofrequency neurotomy: a randomised, double-blind, placebo controlled trial. *Pain* 1997 Oct;**73**(1):15–22.
101. Borrell-Carrió F, Suchman AL, Epstein RM. The biopsychosocial model 25 years later: principles, practice, and scientific inquiry. *Ann Fam Med* 2004 Nov-Dec;**2**(6):576–82.
102. Osuch EA, Willis MW, Bluhm R. CSTS Neuroimaging Study Group, Ursano RJ, Drevets WC. Neurophysiological responses to traumatic reminders in the acute aftermath of serious motor vehicle collisions using [15O]-H2O positron emission tomography. *Biol Psychiatry* 2008 Aug 15;**64**(4):327–35.
103. Eriksson PO, Häggman-Henrikson B, Zafar H. Jaw-neck dysfunction in whiplash-associated disorders. *Arch Oral Biol* 2007 Apr;**52**(4):404–8.
104. Eriksson PO, Zafar H, Häggman-Henrikson B. Deranged jaw-neck motor control in whiplash associated disorders. *Eur J Oral Sci* 2004 Feb;**112**(1):25–32.
105. Grönqvist J, Häggman-Henrikson B, Eriksson PO. Impaired jaw function and eating difficulties in whiplash-associated disorders. *Swed Dent J* 2008;**32**(4):171–7.
106. Woodhouse A, Vasseljen O. Altered motor control patterns in whiplash and chronic neck pain. *BMC Musculoskelet Disord* 2008 Jun 20;**9**:90.
107. Falla D, Bilenkij G, Jull G. Patients with chronic neck pain demonstrate altered patterns of muscle activation during performance of a functional upper limb task. *Spine* 2004 Jul 1;**29**(13):1436–40.
108. Panjabi MM. A hypothesis of chronic back pain: ligament subfailure injuries lead to muscle control dysfunction. *Eur Spine J* 2006 May;**15**(5):668–76.
109. Solomonow M. Sensory-motor control of ligaments and associated neuromuscular disorders. *J Electromyogr Kinesiol* 2006 Dec;**16**(6):549–67.
110. O'Sullivan P. Diagnosis and classification of chronic low back pain disorders: maladaptive movement and motor control impairments as underlying mechanism. *Man Ther* 2005 Nov;**10**(4):242–55.
111. McCabe CS, Haigh RC, Halligan PW, Blake DR. Simulating sensory-motor incongruence in healthy volunteers: implications for a cortical model of pain. *Rheumatology (Oxford)* 2005 Apr;**44**(4):509–16.
112. Winkelstein BA, Santos DG. An intact facet capsular ligament modulates behavioral sensitivity and spinal glial activation produced by cervical facet joint tension. *Spine* 2008 Apr 15;**33**(8):856–62.
113. Ortengren T, Hansson HA, Lövsund P, Svensson MY, Suneson A, Säljö A. Membrane leakage in spinal ganglion nerve cells induced by experimental whiplash extension motion: a study in pigs. *J Neurotrauma* 1996 Mar;**13**(3):171–80.
114. Ohtori S, Moriya H, Takahashi K. Calcitonin gene-related peptide immunoreactive sensory DRG neurons innervating the cervical facet joints in rats. *J Orthop Sci* 2002;**7**(2):258–61. 2002.
115. Dong L, Odeleye AO, Jordan-Sciutto KL, Winkelstein BA. Painful facet joint injury induces neuronal stress activation in the DRG: implications for cellular mechanisms of pain. *Neurosci Lett* 2004 Oct 3;**443**(2):90–4.
116. Tominaga Y, Maak TG, Ivancic PC, Panjabi MM, Cunningham BW. Head-turned rear impact causing dynamic cervical intervertebral foramen narrowing: implications for ganglion and nerve root injury. *J Neurosurg Spine* 2006 May;**4**(5):380–7.
117. Panjabi MM, Maak TG, Ivancic PC, Ito S. Dynamic intervertebral foramen narrowing duringsimulated rear impact. *Spine (Phila Pa 1976)* 2006 Mar 1;**31**(5):E128–34.
118. McBeth J, Chiu YH, Silman AJ, Ray D, Morriss R, Dickens C, et al. Hypothalamic-pituitary-adrenal stress axis function and the relationship with chronic widespread pain and its antecedents. *Arthritis Res Ther* 2005;**7**(5):R992–1000.
119. Gaab J, Baumann S, Budnoik A, Gmünder H, Hottinger N, Ehlert U. Reduced reactivity and enhanced negative feedback sensitivity of the hypothalamus-pituitary-adrenal axis in chronic whiplash-associated disorder. *Pain* 2005 Dec 15;**119**(1–3):219–24.
120. Thornberry NA, Lazebnik Y. Caspases: enemies within. *Science* 1998 Aug 28;**281**(5381):1312–6.
121. Zhang JM, Strong JA. Recent evidence for activity-dependent initiation of sympathetic sprouting and neuropathic pain. *Sheng Li Xue Bao* 2008 Oct 25;**60**(5):617–27.
122. Liu CN, Devor M, Waxman SG, Kocsis JD. Subthreshold oscillations induced by spinal nerve injury in dissociated muscle and cutaneous afferents of mouse DRG. *J Neurophysiol* 2002;**87**:2009–17.
123. England JD, Happel LT, Kline DG, Gamboni F, Thouron CL, Liu ZP, et al. Sodium channel accumulation in humans with painful neuromas. *Neurology* 1996;**47**:272–6.
124. Cummins TR, Dib-Hajj SD, Black JA, Waxman SG. Sodium channels and the molecular pathophysiology of pain. *Prog Brain Res* 2000;**129**:3–19.
125. Kress M, Izydorczyk I, Kuhn A. N- and L- but not P/Q type calcium channels contribute to neuropeptide release from rat skin in vitro. *Neuroreport* 2001;**12**:867–70.
126. White DM, Zimmermann M. The bradykinin-induced release of substance P from nerve fiber endings in the rat saphenous nerve neuroma is not related to electrophysiological excitation. *Neurosci Lett* 1988;**92**:108–13.
127. Dogrul A, Gardell LR, Ossipov MH, Tulunay FC, Lai J, Porreca F. Reversal of experimental neuropathic pain by T-type calcium channel blockers. *Pain* 2003;**105**:159–68.
128. Schaible HG, Schmidt RF. Activation of groups III and IV sensory units in medial articular nerve by local mechanical stimulation of knee joint. *J Neurophysiol* 1983;**49**:35–44.
129. Schaible HG, Schmidt RF. Responses of fine medial articular nerve afferents to passive movements of knee joint. *J Neurophysiol* 1983;**49**:1118–26.
130. Schaible HG, Schmidt RF. Effects of an experimental arthritis on the sensory properties of fine articular afferent units. *J Neurophysiol* 1985;**54**:1109–22.
131. Schaible HG, Schmidt RF. Time course of mechanosensitivity changes in articular afferents during a developing experimental arthritis. *J Neurophysiol* 1988;**60**:2180–95.
132. Kasch H, Qerama E, Bach F, Jensen T. Reduced cold pressor pain tolerance in non-recovered whiplash patients: a 1 year prospective study. *Eur J Pain* 2004;**9**:561–9.
133. Sterling M, Jull G, Kenardy J. Physical and psychological predictors of outcome following whiplash injury maintain predictive capacity at long term follow-up. *Pain* 2006;**122**:102–8.
134. Buitenhuis J, de Jong PJ, Jaspers JP, Groothoff JW. Relationship between posttraumatic stress disorder symptoms and the course of whiplash complaints. *J Psychosom Res* 2006 Nov;**61**(5):681–9.
135. Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 1992;**355**:75–8.

136. Bester H, Beggs S, Woolf CJ. Changes in tactile stimuli-induced behavior and c-Fos expression in the superficial dorsal horn and in parabrachial nuclei after sciatic nerve crush. *J Comp Neurol* 2000;**428**:45–61.
137. Miki K, Zhou QQ, Guo W, Guan Y, Terayama R, Dubner R, et al. Changes in gene expression and neuronal phenotype in brain stem pain modulatory circuitry after inflammation. *J Neurophysiol* 2002 Feb;**87**(2):750–60.
138. Janig W, Habler HJ. Sympathetic nervous system: contribution to chronic pain. *Prog Brain Res* 2000;**129**:451–68.
139. Bossut DF, Shea VK, Perl ER. Sympathectomy induces adrenergic excitability of cutaneous C-fiber nociceptors. *J Neurophysiol* 1996;**75**:514–7.
140. Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. *Neuropharmacology* 1987;**6**:1235–8.
141. Todd AJ. Anatomy of primary afferents and projection neurones in the rat spinal dorsal horn with particular emphasis on substance P and the neurokinin 1 receptor. *Exp Physiol* 2002;**87**:245–9.
142. D'Mello R, Dickenson AH. Spinal cord mechanisms of pain. *Br J Anaesth* 2008;**101**(1):8–16.
143. Kawasaki Y, Zhang L, Cheng JK, Ji RR. Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. *J Neurosci* 2008 May 14;**28**(20):5189–94.
144. Schafers M, Brinkhoff J, Neukirchen S, Marziniak M, Sommer C. Combined epineurial therapy with neutralizing antibodies to tumor necrosis factor-alpha and interleukin-1 receptor has an additive effect in reducing neuropathic pain in mice. *Neurosci Lett* 2001;**310**:113–6.
145. Sorkin LS, Doom CM. Epineurial application of TNF elicits an acute mechanical hyperalgesia in the awake rat. *J Peripher Nerv Syst* 2000;**5**:96–100.
146. Laughlin TM, Bethea JR, Yezierski RP, Wilcox GL. Cytokine involvement in dynorphin induced allodynia. *Pain* 2000;**84**:159–67.
147. Sommer C, Petrausch S, Lindenlaub T, Toyka KV. Neutralizing antibodies to interleukin 1-receptor reduce pain associated behavior in mice with experimental neuropathy. *Neurosci Lett* 1999;**270**:25–8.
148. Miao P, Madec K, Gong Y, Shen H, Eisenstat D, Melanson M, et al. Axotomy-induced up-regulation of tumor necrosis factor-alpha in the dorsal root ganglia. *Neurol Res Neurol Res* 2008 Jul;**30**(6):623–31.
149. Empl M, Renaud S, Erne B, Fuhr P, Straube A, Schaeren-Wiemers N, et al. TNF-alpha expression in painful and nonpainful neuropathies. *Neurology* 2001;**56**:1371–7.
150. Stein C, Clark JD, Oh U, Vasko MR, Wilcox GL, Overland AC, et al. Peripheral mechanisms of pain and analgesia. *Brain Res Rev* 2009 Apr;**60**(1):90–113.
151. Ro LS, Chen ST, Tang LM, Chang HS. Local application of anti-NGF blocks the collateral sprouting in rats following chronic constriction injury of the sciatic nerve. *Neurosci Lett* 1996;**218**:87–90.
152. Ro LS, Chen ST, Tang LM, Jacobs JM. Effect of NGF and anti-NGF on neuropathic pain in rats following chronic constriction injury of the sciatic nerve. *Pain* 1999;**79**:265–74.
153. Cragg BG. What is the signal for chromatolysis? *Brain Res* 1970;**23**:1–21.
154. Zimmermann M. Pathobiology of neuropathic pain. *Eur J Pharmacol* 2001;**429**:23–37.
155. Csillik B, Janka Z, Boncz I, Kalman J, Mihaly A, Vecsei L, et al. Molecular plasticity of primary nociceptive neurons: relations of the NGF-c-jun system to neurotomy and chronic pain. *Ann Anat* 2003;**185**:303–14.
156. Ro LS, Li HY, Huang KF, Chen ST. Territorial and extraterritorial distribution of Fos protein in the lumbar spinal dorsal horn neurons in rats with chronic constriction nerve injuries. *Brain Res* 2004;**1004**:177–87.
157. Hunt SP, Pini A, Evan G. Induction of Fos-like protein in spinal cord neurons following sensory stimulation. *Nature* 1987;**328**:632–4.
158. Hylden JL, Nahin RL, Traub RJ, Dubner R. Effects of spinal kappa-opioid receptor agonists on the responsiveness of nociceptive superficial dorsal horn neurons. *Pain* 1991;**44**:187–93.
159. Lai J, Luo MC, Chen Q, Ma S, Gardell LR, Ossipov MH, et al. Dynorphin A activates bradykinin receptors to maintain neuropathic pain. *Nat Neurosci* Dec 2006;**9**(12):1534–40.
160. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993;**52**:259–85.
161. Liu XG, Sandkuhler J. Long-term potentiation of C-fiber evoked potentials in the rat spinal dorsal horn is prevented by spinal N-methyl-D-aspartic acid receptor blockage. *Neurosci Lett* 1995;**191**:43–6.
162. Moore KA, Kohno T, Karchewski LA, Scholz J, Baba H, Woolf CJ. Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. *J Neurosci* 2002;**22**:6724–31.
163. Passatore M, Roatta S. Influence of sympathetic nervous system on sensorimotor function: whiplash associated disorders (WAD) as a model. *Eur J Appl Physiol* 2006 Nov;**98**(5):423–49.
164. Devor M, Lomazov P, Matzner O. Sodium channel accumulation in injured axons as a substrate for neuropathic pain. In: Boivie J, Hansson P, Lindblom U, editors. *Touch, temperature and pain in health and disease: mechanisms and assessments. Progress in pain research and management series*, vol. 3. Seattle: IASP Press; 1994. p. 207–30.
165. Wall PD, Gutnick M. Properties of afferent nerve impulses originating from a neuroma. *Nature* 1974;**248**:740–3.
166. Devor M. Neuropathic pain: what do we do with all these theories? *Acta Anaesthesiol Scand* 2001;**45**:1121–7.
167. Zhang J-M, Li H, Brull SJ. Perfusion of the mechanically compressed lumbar ganglion with lidocaine reduces mechanical hyperalgesia and allodynia in the rat. *J Neurophysiol* 2000;**84**:798–805.
168. Waxman SG, Cummins TR, Dib-Hajj S, Fjell J, Black JA. HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/10454712" Sodium channels, excitability of primary sensory neurons, and the molecular basis of pain. Muscle Nerve. 1999 Sep;22(9):1177–87.
169. Quinn KP, Lee KE, Ahaghotu CC, Winkelstein BA. Structural changes in the cervical facet capsular ligament: potential contributions to pain following subfailure loading. *Stapp Car Crash J* 2007 Oct;**51**:169–87.
170. Cuellar JM, Montesano PX, Antognini JF, Carstens E. Application of nucleus pulposus to L5 dorsal root ganglion in rats enhances nociceptive dorsal horn neuronal windup. *J Neurophysiol* 2005 Jul;**94**(1):35–48.
171. Anzai H, Hamba M, Onda A, Konno S, Kikuchi S. Epidural application of nucleus pulposus enhances nocireponses of rat dorsal horn neurons. *Spine (Phila Pa 1976)* 2002 Feb 1;**27**(3):E50–5.
172. Woolf CJ, Wall PD. Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *J Neurosci* 1986;**6**:1433–42.
173. Wall PD, Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *J Physiol* 1984 Nov;**356**:443–58.
174. Kellgren JH. On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. *Clin Sci* 1939;**4**:35–46.
175. Feinstein B, Langton JNK, Jameson RM, Schiller F. Experiments on pain referred from deep somatic tissues. *J Bone Jt Surg Am* 1954;**36**:981–97.
176. Graven-Nielsen T. Fundamentals of muscle pain, referred pain, and deep tissue hyperalgesia. *Scand J Rheumatol Suppl* 2006;**122**:1–43.
177. Lumb BM. Inescapable and escapable pain is represented in distinct hypothalamic-midbrain circuits: specific roles for Adelta- and C-nociceptors. *Exp Physiol* 2002 Mar;**87**(2):281–6.
178. Lewis T, Kellgren JH. Observations relating to referred pain, viscero-motor reflexes and other associated phenomena. *Clin Sci* 1939;**4**:47–71.
179. Bogduk N, Marsland A. The cervical zygapophysial joints as a source of neck pain. *Spine* 1988 Jun;**13**(6):610–7.
180. Fukui S, Ohseto K, Shiotani M, Ohno K, Karasawa H, Naganuma Y, et al. Referred pain distribution of the cervical zygapophyseal joints and cervical dorsal rami. *Pain* 1996 Nov;**68**(1):79–83.
181. Cooper G, Bailey B, Bogduk N. Cervical zygapophysial joint pain maps. *Pain Med* 2007 May- Jun;**8**(4):344–53.
182. Aprill C, Dwyer A, Bogduk N. Cervical zygapophyseal joint pain patterns. II: a clinical evaluation. *Spine* 1990 Jun;**15**(6):458–61.
183. Lord SM, Barnsley L, Wallis BJ, Bogduk N. Chronic cervical zygapophysial joint pain after whiplash. A placebo-controlled prevalence study. 4–1745. *Spine* 1996 Aug 1;**21**(15):1737–44. discussion 174.
184. Slipman CW, Plastaras C, Patel R, Isaac Z, Chow D, Garvan C, et al. Provocative cervical discography symptom mapping. *Spine J* 2005 Jul-Aug;**5**(4):381–8.
185. O'Neill CW, Kurgansky ME, Derby R, Ryan DP. Disc stimulation and patterns of referred pain. *Spine* 2002 Dec 15;**27**(24):2776–81.
186. Kasch H, Qerama E, Kongsted A, Bach FW, Bendix T, Jensen TS. Deep muscle pain, tender points and recovery in acute whiplash patients: a 1-year follow-up study. *Pain* 2008 Nov 15;**140**(1):65–73.
187. Hsueh TC, Yu S, Kuan TS, Hong CZ. Association of active myofascial trigger points and cervical disc lesions. *J Formos Med Assoc* 1998 Mar;**97**(3):174–80.
188. Herren-Gerber R, Weiss S, Arendt-Nielsen L, Petersen-Felix S, Di Stefano G, Radanov BP, et al. Modulation of central hypersensitivity by nociceptive input in chronic pain after whiplash injury. *Pain Med* 2004 Dec;**5**(4):366–76.
189. Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. *Curr Rheumatol Rep* 2002 Aug;**4**(4):299–305.
190. Buskila D, Neumann L, Vaisberg G, Alkalay D, Wolfe F. Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury. *Arthritis Rheum* 1997 Mar;**40**(3):446–52.
191. Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, et al. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. *Pain* 2004 Jan;**107**(1–2):7–15.
192. Uhl GR, Sora I, Wang Z. The mu opoiod receptor as a candidate gene for pain: polymorphisms, variations in expression, nociception, and opiate responses. *Proc Natl Acad Sci* 1999;**24**:7752–5.
193. Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 2005 Jan 1;**14**(1):135–43.
194. McLean SA, Diatchenko L, Lee YM, Swor RA, Domeier RM, Jones JS, et al. Catechol O-Methyltransferase haplotype Predicts immediate musculoskeletal neck pain and psychological symptoms after motor vehicle collision. *J Pain* 2011 Jan;**12**(1):101–7.
195. Lafrenière RG, Cader MZ, Poulin JF, Andres-Enguix I, Simoneau M, Gupta N, et al. A dominantnegative mutation in the TRESK potassium channel is linked to familial migraine with aura. *Nat Med* 2010 Oct;**16**(10):1157–60.
196. Schrader H, Stovner LJ, Eisenmenger W. Doubtful nosological validity of the chronic whiplash syndrome. *Orthopade* 2011 Nov 30.
197. Schrader H, Obelieniene D, Bovim G, Surkiene D, Mickeviciene D, Miseviciene I, et al. Natural evolution of late whiplash syndrome outside the medicolegal context. *Lancet* 1996 May 4;**347**(9010):1207–11.

198. Obelieniene D, Schrader H, Bovim G, Miseviciene I, Sand T. Pain after whiplash: a prospective controlled inception cohort study. *J Neurol Neurosurg Psychiatry* 1999 Mar;**66**(3):279–83.
199. Freeman MD, Croft AC, Rossignol AM, Weaver DS, Reiser M. A review and methodologic critique of the literature refuting whiplash syndrome. *Spine* 1999;**24**:86–98.
200. Winkelstein BA. How can animal models Inform on the transition to chronic symptoms in whiplash. *Spine* 2011;**36**:S218–25.
201. Staud R, Robinson ME, Price DD. Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *J Pain* 2007;**8**:893–901.
202. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003 Nov;**60**(11):1524–34.
203. Bogduk N. *Mechanisms of complex regional pain syndromes*. International Spine Intervention Society (ISIS) Societies 14th Annual Scientific Meeting, Salt Lake City, p. 54–70 2006.
204. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet* 1999;**353**:1959–64.
205. Winkelstein BA. Mechanisms of central sensitization, neuroimmunology & injury biomechanics in persistent pain: implications for musculoskeletal disorders. *J Electromyogr Kinesiol* 2004 Feb;**14**(1):87–93.
206. Chien A, Eliav E, Sterling M. Hypoaesthesia occurs with sensory hypersensitivity in chronic whiplash - Further evidence of a neuropathic condition. *Man Ther* 2009 Apr;**14**(2):138–46.
207. Sang CN, Max MB, Gracely RH. Stability and reliability of detection thresholds for human A-Beta and A-delta sensory afferents determined by cutaneous electrical stimulation. *J Pain Symptom Manage* 2003 Jan;**25**(1):64–73.
208. Chien A, Eliav E, Sterling M. Whiplash (grade II) and cervical radiculopathy share a similar sensory presentation: an investigation using quantitative sensory testing. *Clin J Pain* 2008 Sep;**24**(7):595–603.
209. Chien A, Sterling M. Sensory hypoaesthesia is a feature of chronic whiplash but not chronic idiopathic neck pain. *Man Ther* 2010 Feb;**15**(1):48–53.
210. Chien A, Eliav E, Sterling M. The development of sensory hypoesthesia after whiplash injury. *Clin J Pain* 2010;**26**:722–8.
211. Jaggi AS, Singh N. Role of different brain areas in peripheral nerve injury-induced neuropathic pain. *Brain Res* 2011 Jan 13.
212. Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD. Brain activity related to temporal summation of C-fiber evoked pain. *Pain* 2007 May;**129**(1–2):130–42.
213. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol* 2007;**26**:465–73.
214. Meeus M, Nijs J, Van de Wauwer N, Toeback L, Truijen S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: an experimental study. *Pain* 2008 Oct;**139**(2):439–48.
215. Zhuo M. A synaptic model for pain: long term potentiation in the anterior cingulate cortex. *Mol Cells* 2007;**23**:259–71.
216. Elliott J, Pedler A, Kenardy J, Galloway G, Jull G, Sterling M. The temporal development of fatty infiltrates in the neck muscles following whiplash injury: an association with pain and posttraumatic stress. *PLoS One* 2011;**6**(6):e21194.
217. Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. *Clin J Pain* 2000 Jun;**16**(2Suppl):S12–20.
218. Barnsley L, Lord S, Bogduk N. Whiplash injury. *Pain* 1994 Sep;**58**(3):283–307.
219. Taylor JR, Twomey LT. Acute injuries to cervical joints. An autopsy study of neck sprain. *Spine* 1993;**18**:1115–22.